

ORIGINAL ARTICLES

EVALUATION OF THE NEWER THERAPY IN THE PNEUMONIAS*

By ROY E. THOMAS, M. D.
Los Angeles

THE term "newer therapy," as applied to pneumonia, may mean one thing today and something very different tomorrow.

Less than two years ago, specific serum was considered the last word in pneumonia therapy. By its use, the mortality rate from pneumococcus pneumonia, in our larger hospitals, was reduced by 50 per cent. Then came a discovery which has again halved the death rate.

Since Erlich's discovery of salvarsan, we have hoped for a chemical agent which would inhibit or destroy pyogenic organisms *in vivo*; but not until the recent discovery of sulfanilamide was this hope realized. Since then new drugs have been thrown at us so rapidly that confusion has resulted.

ON PROCEDURE

Given a case of pneumonia today, the doctor must ask himself, "Shall I give serum alone, serum with sulfapyridine, sulfapyridine alone, sodium-sulfapyridine, or one of the still newer drugs, sulfathiazole or sulfamethylthiazole?"

If any one, or a combination of these agents, should be selected for use in a given case, how should it be administered? What results are to be expected, and what are the dangerous side effects for which we must be on our guard?

From data gathered in published papers, of which there has been no dearth, from a few reports as yet unpublished, and from a recent visit to several hospitals where large numbers of pneumonias are treated, together with our experience on the pneumonia service at the Los Angeles General Hospital, I have attempted to formulate practical answers to these questions. Tomorrow they may have to be revised.

PATHOGENESIS OF PNEUMONIA

Before discussing therapy, I wish to recall briefly the pathogenesis of pneumonia. When virulent pneumococci invade the lung, they multiply rapidly and spread through the lymph spaces and alveolar septa, until a considerable area is involved. The local reaction to this invasion fills the alveolar spaces with round cells, polymorphonuclear neutrophils, erythrocytes and fibrin, resulting in consolidation. From this point on, without specific therapy, one of two things will occur.

The pneumococci, acting as a good antigen, may cause such a rapid production of antibodies, agglutinins, etc., that by damage to the capsule they are rendered susceptible to phagocytosis, and in a few days spontaneous recovery of the patient occurs. Or because the pneumococci prove to be a poor antigen, as is usually the case with Type III, or

the phagocytic response is poor, because of fatigue, exposure, alcoholism, or advanced age, the infection spreads, finally spills over into the blood stream, and the patient dies of vascular failure or sepsis.

With specific serum and the sulfonamide group of drugs, we can now shorten the illness for the patients who would have recovered spontaneously, and save a large group of patients who otherwise would have died.

The action of specific serum is to furnish quickly antibodies in sufficient amounts for recovery. The action of the sulfonamide group of drugs on the pneumococcus is bacteriostatic, but the mechanism of this inhibitory action is not known. These drugs are definitely not bacteriocidal, as is gramicidin, the promising discovery of Dubos, announced only a few weeks ago. Here is an agent which in high dilution, *in vitro* and *in vivo*, actually kills the pneumococcus, and all other Gram-positive organisms, in short order. Unfortunately, its poor solubility and its toxicity prevent its use in man at this time.

TREATMENT

I wish now to discuss the actual treatment of a pneumococcus pneumonia in which the type of the infecting organism has been determined. And just here let me decry the tendency of many physicians to start chemotherapy without first making a serious effort to obtain a type. After forty-eight hours of treatment the organism may have disappeared from the sputum, or the capsule be so modified that accurate typing is impossible.

If, as has been stated, the action of specific serum is to furnish antibodies, and if the sulfonamide drugs inhibit the growth of pneumococci in the tissues, why should these remedies not have a synergistic action? Indeed, there is much experimental evidence in support of such action, and on the pneumonia service at the Rockefeller Hospital all Type III cases are treated with serum and sulfapyridine from the start. At Harlem Hospital, where every third admission receives both serum and sulfapyridine, the mortality in this group, to date, has been 6.6 per cent, slightly less than that for the group treated with sulfapyridine or its derivatives, and definitely less than the mortality in the group treated with serum alone.

In a recent conversation with two men who have had wide experience and have written much that is considered authoritative on the treatment of pneumonia, each stated definitely that should he be so unfortunate as to contract pneumonia due to any of the lower types of pneumococci, he would wish to be treated with serum and sulfapyridine combined.

Why, then, should we not use such combined treatment in every case where the cost is not prohibitive? I believe that we should, if the patient is not sensitive to serum, and preëxisting renal or liver damage does not contraindicate the use of the drug. Certainly, if for the sake of economy a patient has been started on chemotherapy and fails to respond by a satisfactory drop in temperature, pulse and respirations within thirty-six hours,

* Read before the Fourth General Meeting at the sixtieth annual session of the California Medical Association, Coronado, May 6-9, 1940.

serum should be added and continued until the Francis test indicates a satisfactory antibody response and recovery seems assured.

Also, it would seem wise to use combined serum and drug therapy in all cases with involvement of more than one lobe, in all bacteremic cases, in all those in which the specific soluble substance can be demonstrated in the blood; in patients who appear extremely toxic when first seen, in women who are pregnant, and in the aged.

CHOICE OF DRUG

The choice of a drug may be something of a problem if chemotherapy is determined upon. At present we have only sulfanilamide, sulfapyridine, and its sodium salt, but sulfathiazole will soon be available in private practice. Until then sulfapyridine by mouth seems to be the drug of choice, although Bullowa is using the sodium salt in tablet form, and states that he secures better blood levels with less nausea and vomiting.

When sulfathiazole is approved at Washington, as it probably soon will be, it may prove preferable to sulfapyridine; for in the experience of Blake at the New Haven Hospital, and Flippin and Schwartz at the Philadelphia General, it has proved less toxic and, at the same time, as effective.

If the patient is desperately ill, or even critically ill, and unable to retain adequate amounts of the drug by mouth, the sodium salt should be given intravenously, very slowly in a 5 per cent solution, in distilled water, six-hundredths of a gram per kilogram, and repeated in six hours. Although some of the sodium salt is excreted into the stomach, after one or two injections patients will often tolerate sulfapyridine by mouth. In cases where vomiting persists, two to three grams of sulfapyridine suspended in three ounces of water, and a little starch may be given by rectum. Except in children it is difficult to maintain a satisfactory blood level in this way, and the intravenous administration may have to be resumed.

There has been much controversy over the proper dosage of sulfapyridine and the optimum blood level which we should attempt to maintain. Long, at Johns Hopkins Hospital, advocates an initial dose of four grams. MacLeod, at Rockefeller, starts all cases with one gram. I believe the average initial dose today is two grams. This is followed by one gram every four hours, day and night, until there is a satisfactory response, or a drug-resistant strain of the pneumococcus is encountered. Alkalies are unnecessary, as acidosis does not occur.

When the temperature and pulse have reached a normal level, which often occurs within twenty-four, and usually within forty-eight hours, the drug is continued at six-hour intervals for two days more, after which it is discontinued. This plan gives the average patient about 15 grams of the drug, little more than half the dosage in vogue a year ago.

Owing to irregularity in absorption and excretion, and the conjugation of varying amounts after absorption, into acetylsulfapyridine, it is dif-

ficult by any plan of administration to keep the free active drug at any desired level in the blood stream. Four to eight milligrams per cent seems to be a very satisfactory level, but many cases do well in which this level is never attained. In taking sulfapyridine blood-level readings, it is important to take the blood in the same time relation to the last dose of the drug.

TOXIC MANIFESTATIONS OF SULFONAMIDE GROUP

The tendency to reduce the average total amount of sulfapyridine given undoubtedly has resulted from the accumulating data on its side effects, which are always unpleasant, frequently alarming, and occasionally fatal. I shall briefly mention these toxic manifestations of the sulfonamide group, for they should all be kept in mind whenever the drug is being used.

As has been said, nausea and vomiting may be so troublesome as to require rectal or intravenous medication. Pulverizing the tablets and mixing the powder with various food substances, such as milk and gruel, may be helpful. Occasionally a five-grain capsule of chloratone with each dose of sulfapyridine has seemed to be of benefit. Alkalies have been of no value in our experience.

Cyanosis occurs less frequently and is less marked than with sulfanilamide. It is not a contraindication to the continued use of sulfapyridine or sulfathiazole.

A drug rash sometimes occurs and seems to be particularly severe in patients who are exposed to strong sunlight.

Drug fever is a toxic manifestation, which is not always easily recognized. If it is suspected, the drug should be discontinued until the cause of fever can be determined.

Toxic hepatitis with jaundice is not uncommon in pneumonia. However, should it appear during the administration of any of the sulfonamide group the drug, in my judgment, should be discontinued. The same applies to toxic psychoses, which are not rare. Vertigo, headache, and marked depression may occur.

The truly serious conditions resulting from sulfonamide therapy appear in the blood and in the urinary tract. If possible, daily blood counts should be made. Leukopenia, at the onset of pneumonia, is not a contraindication for chemotherapy. However, should a marked drop in the white cells, especially the neutrophils, occur during treatment, the drug should be stopped immediately. Acute hemolytic anemia may occur. The hemoglobin and red cell count may drop very rapidly—another reason for frequent blood counts in these patients. Polychromatophilia may be the first sign of blood destruction, and is an indication to stop treatment and alkalinize the urine. The hemoglobin and red count may drop to 50 per cent of normal, or even lower, if transfusions are not given early and frequently.

The renal complications of sulfapyridine therapy seem to be unique. They consist, primarily, of mechanical blocking of the renal tubules, and even

the kidney pelvis and ureters, with masses of acetylsulfapyridine crystals. The first indication of this serious condition may be abdominal pain from ureteral colic, numerous blood cells in the urine, or frank hematuria. Some degree of hematuria is said to occur in 5 per cent of cases receiving sulfapyridine. If this is generally true, we must have overlooked it a number of times. Azotemia may occur, and any sudden drop in the urinary output demands prompt investigation. Cases have been reported in which kidney function was re-established and the patient's life saved by ureteral lavage.

PNEUMONIA SERVICES AT LOS ANGELES GENERAL HOSPITAL

In the year 1939 three hundred thirty-one adults with pneumococcus pneumonia were treated with chemotherapy, serum or both, on the two Pneumonia Services at the Los Angeles General Hospital, with a mortality of 13 per cent, the lowest rate for this hospital since satisfactory records have been kept. The first four months of 1940 have shown a further drop in mortality to approximately 10 per cent.

OTHER PNEUMONIAS

What has been said up to this point applies only to the pneumonias in which the pneumococcus is the infecting organism. The time allowed me will permit only brief mention of the results with chemotherapy in the pneumonias of other etiology.

Fair results have been reported from the use of sulfanilamide and sulfapyridine in hemolytic streptococcus pneumonias. We have seen little or no benefit in streptococcus viridans infections.

Sulfamethylthiazole is said to be efficacious in staphylococcus infections, but in four staphylococcus pneumonias recently observed—one with a positive blood culture—this drug seemed to be of little value until polyvalent staphylococcus antitoxin was added to the treatment. All four of these patients recovered. Because of the frequency of multiple neuritis following the use of sulfamethylthiazole it will probably not be released for general distribution.

We have had no experience with tularemic pneumonia, but Richards of Salt Lake City has recently reported that sulfanilamide is of benefit in these cases.

A few scattered reports on the treatment of Friedlander's infection with chemotherapy have recently appeared and are most encouraging. In the past few months we have treated, with sulfapyridine, three Friedlander's pneumonias, one with a strongly positive blood culture and one with cavitation. All three were desperately ill. All recovered.

As might be expected, virus pneumonias do not seem amenable to chemotherapy.

IN CONCLUSION

In summary, it can safely be said that chemotherapy is of definite value in nearly all types of pneumonia. When judiciously used alone, or in conjunction with specific serum, it has resulted

in a remarkable reduction in the mortality from pneumococcus pneumonia. I venture to predict that within a year the death rate from this disease, even in our large charity hospitals, will drop below 10 per cent; and pneumonia, instead of ranking fourth among the causes of death, will be pushed far down the list.

1136 West Sixth Street.

SURGICAL TREATMENT OF ESSENTIAL HYPERTENSION*

By WHITFIELD CRANE, M.D.
Oakland

THE medical treatment of progressive essential hypertension, in most instances, has been so unsuccessful in the past that it is only natural that surgical procedures for the relief of this grave condition should have been added to our therapeutic armamentarium. These surgical procedures have been employed for a sufficient length of time for us to estimate their efficacy and evaluate the results. Statistical data thus far show the mortality to be extremely low, that there is no resultant disability of any consequence, and that the clinical results in a certain percentage of selected cases have been of great value.

The importance of the work, study, and accumulated experimental and clinical evidence that has been compiled is apparently underestimated by the profession as a whole. Just why this should be it is difficult to say. True, all new surgical procedures, and especially those that are extensive in character, are, and should be, looked upon with a certain amount of healthy constructive skepticism. In the light of the clinical data at hand on this subject, however, it is hard to explain the antagonism which is displayed by a large section of the profession toward these newer procedures.

Every physician knows that the medical treatment of progressive essential hypertension, with the exception of those cases sensitive to potassium sulphocyanate, has been anything but satisfactory. If anyone doubts this, let him consult the files of the ever-increasing number of physicians who themselves are submitting to surgical relief of hypertension. Why, then, condemn some new method of approach because the results are not 100 per cent perfect? I am quite sure that most physicians would be pleased if they could get the results medically that have been and are being obtained with surgery. We do not hesitate to recommend surgical procedures in the therapy of cancer if there is the slightest hope of operability. Progressive hypertension is just as dangerous and much more prevalent than cancer. It is not logical to deny these people what relief surgery may offer.

THEORETICAL CONSIDERATIONS

The true cause of primary essential hypertension is not as yet known. We do not presume to state, therefore, that we can remove the cause and cure hypertension surgically, any more than we can state

* Read before the Alameda County Medical Society, Oakland, California, November 20, 1939.